REMARKS

The application includes claims 1-15 and 17. Claims 1 and 17 are hereby amended.

The present invention involves detecting a dye bolus during its transit through an observed region of the body. In order to do so, tissue through which the dye will transit is illuminated by means of a suitable excitation radiation (radiation that excites the dye) and fluorescence radiation caused by excitation of the dye in the bolus is detected. Of note, the due that is used is non-specific, i.e. it does not bind to specific cells and its fluorescence output does not depend on activation e.g. by enzyme cleavage. Rather, the non-specific dye simply transits or moves through the tissue. The dye bolus is detected during it transit, and the time required for transit (in the order of seconds to minutes) is measured. (The transit time may also be referred to as "macrotime T"). The transit time will vary, depending on the condition of the tissue, e.g. in cases of reduced blood perfusion, for example as a result of partial occlusion of arteries, the bolus takes longer to reach a target area (paragraph [0003] fo the published application). In addition, the time between the initiation of optical excitation radiation and the occurrence of fluorescence radiation caused by the excitation radiation ("flight time of the fluorescence photons") is measured or monitored as the bolus makes its transit. This time may also be referred to as "microtime t", and is on the order of picoseconds. These two values (transit time of the bolus and flight time of the fluorescence photons, depicted in graphical form in Figures 3 and 4 of the application) are used to obtain a time profile. The time profile is a function of the mean flight time of the fluorescence photons over the transit time, and is evaluated in order to determine some property of the tissue through which the dye bolus transits (e.g. perfusion, thickness of tissue, etc.). An exemplary embodiment of the invention is described in paragraph [0015] of the published application (US 2007/0255134 A1).

It should be noted that the determination of the flight time of fluorescence photons for a dye bolus that does not specifically bind to cells but is instead a blood pool agent allows a determination of the depths of tissue from which the fluorescent radiation of the dye bolus emanates. This allows detection of the passage of the dye bolus. For example, when examining head tissues such as the brain, it can be determined that the bolus enters the cortex before it enters the extracerebral layers, (see paragraph [0008] as well as [0036] and [0037] of the present application s published.

Claim 1 is hereby amended to recite that the fluorescent dye that is utilized is non-

specific, and that both measurements (the time required for transit of the bolus through the tissue, and the flight times of the fluorescence photons that are monitored as the bolus is passing through the tissue) are used to obtain a profile of the photon flight time over the transit time of the dye bolus. The profile is in turn used to evaluate the tissue through which the bolus has passed. Different photon flight times will be noted for tissues having different properties, depending e.g. on the extent of perfusion, thickness of tissue, etc. These amendments do not add new matter, support being found, for example, in paragraphs [0015], [0031] and [0035] and in Figure 3.

Claim Rejections: 35 USC § 102(e)

Claims 1, 3, 4, 7, 8, 11, 13, 14 and 17 stand rejected as anticipated by Sevick-Mauraca (U.S.7,3628,059). This rejection is traversed.

In contrast to the present invention, Sevick teaches an imaging technique for obtaining an image of tissues in a non-invasive manner. Sevick does not disclose the observation, over time, of a dye bolus during its transit. Rather, Sevick discloses using a dye as a fluorescent contrast agent which serves to map spatial variations in dye distribution in the tissue. Sevick evaluates the phase of the florescent radiation compared with the phase of the exciting radiation (see claim 18). However, the phase (time) relation between the high frequency signals serves to characterize the tissue by means of its scattering properties. No profile of the time of flight measurements *over time* is established (i.e. transit time of the dye bolus through tissue is not measured) . Instead, the mapping of the tissue is a steady state process and not a dynamic process, as is the method of the present invention. Consequently, Sevick fails to teach the forming of a profile of the time of flight measurements *during the time when the dye bolus transits*.

Examples of the images generated by Sevick are provided in Figures 10-14, 21A-C and 22A-D. Applicant draws Examiner's attention, in contrast, to Figures 3 and 4 of the present application which show data obtained using the method of the invention. As is clearly seen, the x axis of Figures 3 and 4 is time of transit of the dye bolus.

Sevick does not calculate a profile of the photon flight time over the transit time of the dye bolus, and does not collect the necessary data to do so (i.e. the transit of the bolus is not monitored or measured). Indeed, Sevick has no reason to do so. Rather, the technology of Sevick is designed to produce an "image" (i.e. a pictorial representation or "picture", as shown in Figures 10-14, 21A-C and 22A-D) of the tissues by detecting the stationary distribution of fluorescence at the particular time at which a fluorescence measurement is

made. This does not require or use data generated by monitoring the movement of dye through tissue with time. Rather, a snapshot of the pattern of the stationary distribution of fluorescence is obtained. In fact, a dye, which is required in the present invention, is not necessarily required by Sevick, as endogenous fluorescence may be detected instead (see next to last sentence of the Abstract, and last sentence of first paragraph of column 7). This is because, in contrast to the present invention, Sevick does not monitor the movement of the dye bolus itself, whereas claims 1 and 17 require that the movement (transit) time of the dye bolus be measured and used in the profile that is established. The only references to "time" or "time based measurements" in Sevick are those which involve fluorescence half life and photon time of flight. However, these refer to properties of the fluorescence itself at any given instant, and have nothing to do with the physical movement of the bolus through tissue. The device of Sevick does not contain any means to monitor or track the progress of the actual transit of the bolus of dye through tissue.

Thus, Sevick clearly does not anticipate the claimed subject matter of the present application.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections: 35 USC § 103(a)

Claims 2 and 12 stand rejected under 35 USC § 103(a) as obvious over Sevick (as above) in view of Ntziachristos (6,615,063). This rejection is traversed.

The defects of Sevick as an anticipatory reference are described in detail above. Briefly, Sevick does not monitor the time of transit of the dye bolus through tissue, and then combine this data with fluorescence measurements to achieve a profile over time. Rather, Sevick creates an image of the stationary distribution of fluorescence within tissues at a particular point in time.

As stated by Examiner, Ntziachristos teaches only emitting an excitation radiation pulse with a pulse width in the picosecond image using fluorescence-mediated molecular tomography system. This is in the context of teaching molecular imaging which uses quenched fluorochromes. The fluorochromes are activated by specific interactions, e.g. by specific enzymes. For this purpose, a specific fluorescent dye is needed which has a target substrate which specifically binds to the target materials (see column 8, line 65 to column 9, line 4). In contrast, the present invention used a non-specific dye which does not bind to specific cells. In addition, the approach of Ntziachristos is similar to that of Sevick, and does

not involve measuring dye bolus transit as an observation port so that no time profile of measured values is obtained. Clearly, Ntziachristos fails to cure or mitigate the defects of Sevick in any way, and no combination of Ntziachristos and Sevick renders the present invention as recited in claims 2 and 12, obvious.

Claim 9 stands rejected under 35 USC § 103(a) as obvious over Sevick (as above) in view of Boas (US 7,328,059).This rejection is traversed.

The defects of Sevick with as an anticipatory reference are described in detail above and summarized in the preceding section. Boas teaches only administering a dye bolus into the blood stream of a patient to monitor the brain. Boas fails to teach a flights time determination and the evaluation of a flight time profile during transit of a dye bolus, and thus does not cure or mitigate in any way the defects of Sevick. Thus, no combination of Boas and Sevick render the present invention as claimed in claim 9 obvious.

Claim 10 stands rejected under 35 USC § 103(a) as obvious over Sevick (as above) in view of Zhao (US 2003/0031628).This rejection is traversed.

The defects of Sevick with as an anticipatory reference are described above. Zhao teaches only injecting mice suffering from tumors with dye, and detecting fluorescence of the tumors in the lungs of the mice. Zhao does not describe monitoring the transit of the dye bolus, or obtaining a profile that is a ratio of photon time of flight to bolus transit time, as a way of evaluating tissue condition. Zhao thus does not cure or mitigate in any way the deficiencies of Sevick as a reference, and no combination of Zhoa and Sevick render the present invention as claimed in claim 10 obvious.

Claims 5, 6 and 15 stand rejected under 35 USC § 103(a) as obvious over Sevick (as above) in view of Folestad (US 6,794,670).This rejection is traversed.

The defects of Sevick with as an anticipatory reference are described above. Folestad teaches only detecting radiation reflected from a sample as well as diffusely backscattered radiation by a single lens in a time-resolved manner. Folestad does not describe monitoring the transit of a dye bolus, or obtaining a profile that is a ratio of photon time of flight to bolus transit time, as a way of evaluating tissue condition. Folestad thus does not cure or mitigate in any way the deficiencies of Sevick as a reference, and no combination of Folestad and Sevick render the present invention as claimed in claim 10 obvious.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of these rejections.

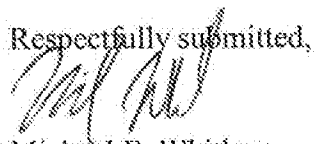
Concluding Remarks

In view of the foregoing, it is respectfully requested that the application be reconsidered, that claims 1-15 and 17 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

A provisional petition is hereby made for any extension of time necessary for the continued pendency during the life of this application. Please charge any fees for such provisional petition and any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,



Michael E. Whitham
Reg. No. 32,635

Whitham, Curtis, Christofferson & Cook, P.C.
11491 Sunset Hills Road, Suite 340
Reston, VA 20190
Tel. (703) 787-9400
Fax. (703) 787-7557
Customer No.: 30743